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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte DEB K. CHATTERJEE and MARY C. LONGO

Appeal 2009-002944
Application 10/091,538
Technology Center 1600

Decided: January 4, 2010

Before TONI R. SCHEINER, DONALD E. ADAMS, and
RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims 1, 16, 17, 28, 30, 41, 51-55, 57, 60-62, 69, 70, 77, 78, 85-87, and 91-96, the only claims pending in this application. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

The claims are directed to an *in vitro* protein or nucleic acid synthesis system (claims 1, 16, 17, 28, 30, 55, 61, 62, and 85-87); a kit for *in vitro* synthesis (claims 41, 57, 69, 70, and 91-93); and a composition (claims 51-54, 60, 77, 78, and 94-96). Claims 1, 61, and 86 are illustrative:

1. An *in vitro* protein or nucleic acid synthesis system comprising: at least one extract from an E. coli cell having a mutation that results in reduced activity of at least one nuclease, wherein said E. coli cell does not express Gam, wherein said at least one extract is modified by the addition of Gam protein.

61. The *in vitro* protein or nucleic acid synthesis system of claim 1, wherein said nuclease is a DNase.

86. The *in vitro* synthesis system according to claim [1, comprising at least two different energy sources, wherein each of the at least two different energy sources generates or regenerates high energy triphosphate compounds for the synthesis], wherein the at least two different energy sources are selected from the group consisting of pyruvate, phosphoenolpyruvate (PEP), carbamoyl phosphate, acetyl phosphate, creatine phosphate, phosphopyruvate, glyceraldehyde-3-phosphate and glucose-6-phosphate.

The Examiner relies on the following evidence:

Kudlicki et al.	US 6,664,379 B1	Dec. 16, 2003
Swartz et al.	WO 00/55353 A1	Sep. 21, 2000

Daiguan Yu, et al., *An efficient recombination system for chromosome engineering in Escherichia coli*, 97 PROC. NATL. ACAD. SCI. 5978-5983 (2000).

Julie M. Pratt, *Coupled Transcription-Translation in Prokaryotic Cell-Free Systems*, in Transcription and Translation: a Practical Approach 179-209 (B.D. Hanes, et al. eds., publisher unknown) (1984).

The rejections presented by the Examiner follow:

1. Claims 1, 16, 17, 28, 30, 41, 51-55, 57, 60, 85, 91, and 94 rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Pratt and Yu.
2. Claims 86, 87, 92, 93, 95, and 96 rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Pratt, Yu, and Swartz.
3. Claims 61, 62, 69, 70, 77, and 78 rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Pratt, Yu, and Kudlicki.

We affirm.

PRINCIPLES OF LAW

"[T]he [E]xaminer bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). On appeal to this Board, Appellants must show that the Examiner has not sustained the required burden. *See Ex parte Yamaguchi*, 88 USPQ2d 1606, 1608 and 1614 (BPAI 2008) (precedential); *Ex parte Fu*, 89 USPQ2d 1115, 1118 and 1123 (BPAI 2008) (precedential).

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). It is proper to "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418. *See also id.* at 421 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton.").

> If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it

> would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.

Id. at 417.

In sum, the "suggestion test is in actuality quite flexible and not only permits, but *requires*, consideration of common knowledge and common sense." *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1367 (Fed. Cir. 2006).

Argument by counsel cannot take the place of evidence. *In re Cole*, 326 F.2d 769, 773 (CCPA 1964); *In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997).

"'[I]t is not inventive to discover the optimum or workable ranges by routine experimentation.'" *In re Geisler*, 116 F.3d at 1470 (quoting *In re Aller*, 220 F.2d 454, 456 (CCPA 1955)).

Arguments not made are waived. *See* 37 C.F.R. § 41.37(c)(1)(vii).

The combination of Pratt and Yu:

ISSUE

Have Appellants established error in the Examiner's prima facie case of obviousness?

FINDINGS OF FACT

FF 1. Pratt teaches "coupled transcription-translation in prokaryotic cell-free systems" (Pratt 179: Title and 11-15).

FF 2. Pratt teaches two coupled transcription-translation systems: (1) the *E. coli* S30 extract system of Zubay and (2) the Gold and Schweiger system (Pratt 179: 15-17).

FF 3. Pratt teaches that the Gold and Schweiger system is "as widely used as the Zubay system" (Pratt 190: 32-33). Notwithstanding the widespread use of both systems we limit our discussion to the Zubay system.

FF 4. Pratt teaches that "[t]he cell-free system devised by Zubay . . . involves the preparation of a crude extract from *E. coli* which contains all the enzymes and factors necessary for transcription and translation, although the extract must be supplemented with amino acids, an energy regenerating system and certain cofactors" (Pratt 179: 22-25).

FF 5. Pratt teaches that "*E. coli* strain MRE600 is favoured as the source of S30 extract for routine identification of gene products using plasmids or phage λ as the DNA template" (Pratt 183: 2-4; *see also* Ans. 5).

FF 6. Appellants do not dispute and therefore concede to the Examiner's finding that *E. coli* strain MRE600 has a mutation in RNase E, "but is wild type for the production of the RecBCD exonuclease" (Ans. 5).

FF 7. Pratt teaches that a degradation problem arises when using linear DNA templates in a coupled transcription-translation system that uses an extract obtained from *E. coli* strain MRE600 due to the presence of exonuclease V, the product of the product of the "*recB* and *recC* genes" (Pratt 200: 23-24 and 39-40; *see also* Ans. 4-5).

FF 8. Pratt teaches that this problem in Zubay's system is overcome by using a extract from "a temperature-sensitive *recB* strain" of *E. coli*, wherein the coupled transcription-translation is performed at a temperature that renders exonuclease V inactive (Pratt 201: 7-14; *see also* Ans. 4).

FF 9. Yu teaches "that mutant *recBCD* [*E. coli*] strains have been used to prevent the rapid degradation of linear DNAs but that such strains lacking the RecBCD exonuclease are extremely poor growing" (Ans. 5; *see* Yu 5978: col. 1, ll. 23-25).

FF 10. Yu teaches that "Gam inhibits the RecBCD nuclease from attacking linear DNA" (Yu 5978: col. 2, ll. 18-19; Ans. 5 and 9) and teaches expressing Gam from a prophage in its system (Yu 5981: col. 2).

FF 11. The Examiner finds that "neither Pratt nor Yu . . . make an explicit statement which suggests adding the Gam protein to" the extract of an in vitro protein or nucleic acid synthesis system (Ans. 9-10).

FF 12. Appellants' Specification discloses that

> Inhibitors can be used or included in the systems of the invention by any known method. For example, inhibitors may be added to the system before, during or after introduction of the nucleic acid template. Inhibitors can also be transcribed or expressed in a cell used to prepare the extract or transcribed or expressed during the protein synthesis reaction.

(Spec. 15: ¶[0045].)

ANALYSIS

The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Claim 1 is representative. Claim 1 is drawn to an in vitro protein or nucleic acid synthesis system. The system of claim 1 comprises at least one extract from an *E. coli* cell having a mutation that results in reduced activity of at least one nuclease, wherein said *E. coli* cell does not express Gam, wherein said at least one extract is modified by the addition of Gam protein.

The Examiner finds and Appellants do not dispute that Pratt teaches an in vitro protein or nucleic acid synthesis system (FF 1-5). The Examiner finds and Appellants do not dispute that Pratt's system comprises at least one extract from an E. coli cell that (i) has a mutation that results in reduced activity of at least one nuclease (RNase E) and (ii) does not express Gam (FF 4-6). Appellants do not dispute that Yu teaches that "Gam inhibits the RecBCD nuclease from attacking linear DNA" (FF 10). Appellants do not dispute the Examiner's finding that both Pratt and Yu teach that exonuclease V degrades linear DNA (FF 7-9).

Based on the foregoing facts (FF 1-10) the Examiner concludes that it would have been prima facie obvious to a person of ordinary skill in this art at the time of Appellants' claimed invention to utilize a linear DNA template in a coupled transcription-translation system as taught by Pratt, wherein the extract from the *E. coli* MRE600 strain is supplemented with Gam protein, which as taught by Yu inhibits the activity of exonuclease V (*see* Ans. 6).

The Examiner does not dispute Appellants' contention that neither Pratt nor Yu teach the addition of Gam protein to an in vitro protein or nucleic acid synthesis system (*Cf.* App. Br. 9-10 and FF 11). Nevertheless, the Examiner reasons that both Pratt and Yu recognize the problem associated with exonuclease V (Ans. 10-11; *see also* FF 7-9) and while Pratt solved the problem by use of a mutant *E. coli* (FF 8), Yu solved the problem by expressing Gam from a prophage (FF 8, Ans. 11; and FF 10). Nevertheless, Appellants contend that Yu

> [T]each[es] expression of a protein (Gam) within a live cell that is engineered to contain and express the Gam gene, and, further, the cell that is engineered by Yu . . . to express the Gam gene also produces the enzyme (recBC) that is to be inhibited by the

> in vivo synthesized protein (Gam). Thus, Yu . . . do[es] not disclose an extract, do[es] not teach addition of anything to any extract, and certainly do[es] not teach the addition of a protein to an extract.

(App. Br. 10.) We are not persuaded.

While it is true that Yu teaches the expression of Gam in vivo, Appellants concede that Yu teaches that Gam inhibits exonuclease V, the recBC gene product (*id.*; *see also* FF 10). Accordingly, Appellants' position appears to be that instead of adding Gam to an *E. coli* extract as required by the claimed invention, the combination of Pratt and Yu suggest modifying *E. coli* to express Gam and then using this modified bacterium to prepare an extract containing Gam. On this point, the Examiner has the better argument.

Directing attention to "[p]aragraph [0045] on page 15 of . . . [Appellants'] specification" (Ans. 12; FF 12) the Examiner reasons that

> There would be no real distinction between a cell extract made by transforming a cell with a heterologous gene, culturing the cell so as to express the gene and making an extract and an extract made by culturing an otherwise similar cell which is not transformed, making a cell extract and then adding an amount of the same protein produced by the heterologous gene to the cell extract.

(Ans. 11.) We agree and find no error in the Examiner's reasoning that the combination of Pratt and Yu suggest, to a person of ordinary skill in this art, the addition of Gam protein to the *E. coli* extract component of an in vitro protein or nucleic acid synthesis system to inhibit exonuclease V activity (*see* Ans. 6). Accordingly, we are not persuaded by Appellants' unsupported contention that

> At the time the invention was made, it was not known whether addition of Gam protein to an E. coli cell extract would protect linear DNA molecules from degradation or if the use of Gam protein in an in vitro synthesis system would adequately reduce or eliminate recBC activity, or whether it would interfere with transcription and/or translation.

(App. Br. 10.) To the contrary, we find that a person of ordinary skill in the art with knowledge that Gam protein will inhibit the activity of exonuclease V would have determined the optimum or workable range of Gam protein to add to an *E. coli* extract through the exercise of routine experimentation. *Geisler*, 116 F.3d at 1470. There is no persuasive evidence on this record to support a contrary conclusion. Argument by counsel cannot take the place of evidence. *Cole*, 326 F.2d at 773; *Geisler*, 116 F.3d at 1471.

CONCLUSION OF LAW

Appellants failed to established error in the Examiner's prima facie case of obviousness.

The rejection of claim 1 under 35 U.S.C § 103(a) as unpatentable over the combination of Pratt and Yu is affirmed. Claims 16, 17, 28, 30, 41, 51-55, 57, 60, 85, 91, and 94 fall together with claim 1.

The combination of Pratt, Yu, and Swartz:

ISSUE

Have Appellants established error in the Examiner's prima facie case of obviousness?

FINDINGS OF FACT

FF 13. The Examiner relies on the combination of Pratt and Yu as discussed above (Ans. 6).

FF 14. The Examiner finds that the combination of Pratt and Yu fails to teach the use of two "different energy sources selected from the group consisting of pyruvate, [phosphoenolpyruvate] (PEP), carbamoyl phosphate, acetyl phosphate, creatine phosphate, phosphopyruvate, glyceraldehydes-3-phosphate and glucose-6-phosphate" (Ans. 6-7).

FF 15. Appellants do not dispute and therefore concede to the Examiner's finding that Swartz makes up for the foregoing deficiency (*see* FF 14) in the combination of Pratt and Yu (Ans. 7).

ANALYSIS

The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Claim 86 is representative.

Based on the foregoing facts (FF 13-15) the Examiner concludes that "it would have been obvious to one of ordinary skill in the art to substitute the energy generating systems of Pratt . . . with the systems disclosed by Swartz" (Ans. 7).

Appellants do not dispute and therefore concede to the Examiner's finding that Swartz makes up for failure of the combination of Pratt and Yu to suggest the use of two "different energy sources selected from the group consisting of pyruvate, [phosphoenolpyruvate] (PEP), carbamoyl phosphate, acetyl phosphate, creatine phosphate, phosphopyruvate, glyceraldehydes-3-phosphate and glucose-6-phosphate" (FF 14-15).

Instead, Appellants contend that "Swartz does not make up for the deficiencies of Pratt and Yu" because Swartz "does not disclose or suggest Gam protein or the addition of Gam protein to an E. coli lysate" (App. Br. 11). For the reasons set forth above with regard to claim 1 we find no deficiency in the combination of Pratt and Yu with regard to the addition of Gam protein to an *E. coli* extract. Accordingly, we are not persuaded by Appellants' contention to the contrary.

CONCLUSION OF LAW

Appellants failed to establish error in the Examiner's prima facie case of obviousness.

The rejection of claim 86 under 35 U.S.C § 103(a) as unpatentable over the combination of Pratt, Yu, and Swartz is affirmed. Claims 87, 92, 93, 95, and 96 fall together with claim 86.

The combination of Pratt, Yu, and Kudlicki:

ISSUE

Have Appellants' established error in the Examiner's prima facie case of obviousness?

FINDINGS OF FACT

FF 16. The Examiner relies on the combination of Pratt and Yu as discussed above (Ans. 7-8).

FF 17. The Examiner finds that the combination of Pratt and Yu fails to teach the use of "an extract of an *E. coli* strain deleted for one or more DN[a]ses" (Ans. 8).

FF 18. Appellants do not dispute and therefore concede to the Examiner's finding that Kudlicki makes up for the foregoing deficiency (*see* FF 17) in the combination of Pratt and Yu (*id.*).

ANALYSIS

The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Claim 61 is representative.

Based on the foregoing facts (FF 16-18) the Examiner concludes that "it would have been obvious to one of ordinary skill in the art to delete the genes encoding one or more DNases of *E. coli* to reduce the DNase activity [in] . . . the . . . extract" (Ans. 8).

Appellants do not dispute and therefore concede to the Examiner's finding that Kudlicki makes up for failure of the combination of Pratt and Yu to suggest "an extract of an *E. coli* strain deleted for one or more DN[a]ses" (FF 17-18).

Instead, Appellants contend that "Kudlicki does not make up for the deficiencies of Pratt and Yu" because "Kudlicki does not disclose Gam protein" (App. Br. 11-12). For the reasons set forth above with regard to claim 1 we find no deficiency in the combination of Pratt and Yu with regard to the addition of Gam protein to an *E. coli* extract. Accordingly, we are not persuaded by Appellants' contention to the contrary.

CONCLUSION OF LAW

Appellants failed to establish error in the Examiner's prima facie case of obviousness.

The rejection of claim 61 under 35 U.S.C § 103(a) as unpatentable over the combination of Pratt, Yu, and Kudlicki is affirmed. Claims 62, 69, 70, 77, and 78 fall together with claim 61.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

cdc

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